CD131 BINDING PROTEINS AND USES THEREOF

RELATED APPLICATION DATA

[0001] The present application is a continuation of U.S. patent application Ser. No. 15/779,252, filed Nov. 5, 2018 and issued as U.S. Pat. No. 10,894,834, which is the U.S. national stage entry under 35 U.S.C. § 371 of International Application No. PCT/AU2016/051158, filed on Nov. 25, 2016, which claims priority to Australian Patent Application No. 2015904924, filed on Nov. 27, 2015. The contents of these applications are each incorporated herein by reference in their entirety.

SEQUENCE LISTING

[0002] The present application is filed with a Sequence Listing in electronic form. The entire contents of the Sequence Listing are hereby incorporated by reference.

FIELD

[0003] The present disclosure relates to CD131-binding proteins and compounds and uses thereof.

BACKGROUND

[0004] The pleiotropic cytokines interleukin (IL)-3 (IL-3), IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF) play critical and overlapping roles in the differentiation and function of myeloid cells. They are important mediators of host defense and innate immunity, but can also contribute significantly to the development and progression of inflammatory pathologies including inflammatory airway diseases such as asthma, chronic rhinosinusitis with and without nasal polyposis (CRSwNP, CRSsNP), chronic obstructive pulmonary disease (COPD) and asthma-COPD overlap syndrome (ACOS). GM-CSF has also been implicated in autoimmune conditions, such as rheumatoid arthritis and IL-3 has been implicated in conditions, such as leukemia. In asthma and COPD, GM-CSF expression is elevated in sputum, bronchoalveolar lavage fluid (BALF) and bronchial biopsies. IL-3 acts at the early stages of hematopoiesis and synergizes with other growth factors for hemopoietic development. It also modulates the activity of mature cell types such as monocytes, dendritic cells, megakaryocytes, mast cells and can activate eosinophils and prime basophils to release histamine. A growth factor for basophils, increased levels of IL-3 in BALF are typically present after allergen challenge. IL-5 is more cell type-specific, regulating the production and release of mature eosinophils from the bone marrow into the circulation. Elevated levels of IL-5 have been found in the serum and airway fluid of patients with asthma. In asthmatic subjects, IL-5 inhalation increased AHR as well as the recruitment of activated eosinophils to the airways.

[0005] Each of IL-3, IL-5 and GM-CSF all signal through a multimeric receptor made up of a common β chain (β_c chain or CD131) and a cytokine specific α chain.

[0006] As a consequence of the evidence supporting a key role for cells of the myeloid lineage and IL-3, IL-5 and GM-CSF in the development and progression of inflammatory airway disease, a number of therapeutic antibodies targeting individual cytokines or receptor α-chains are in clinical development. While these agents may prove useful in selected subsets of patients it is likely that their broader application will be limited by both the redundant and overlapping function of the molecules that they target and by the variable nature of the inflammatory cell infiltrate that can underpin asthma. For example, studies of the anti-IL-5 antibody mepolizumab have shown that targeting only IL-5 has no effects on airway obstruction or airway hyperresponsiveness in patients with asthma.

[0007] It will be clear to the skilled artisan based on the foregoing that there is a need in the art for compounds (e.g., antibodies and antibody-derived proteins) that can treat conditions mediated by IL-3, IL-5 and/or GM-CSF.

SUMMARY

[0008] In producing the present invention, the inventors sought to produce reagents (e.g., antibodies and proteins comprising antigen binding domains thereof) that bind to CD131 and neutralize signaling by IL-3, IL-5 and GM-CSF. The inventors produced a series of antibodies having such activity, some of which potently neutralize signaling by IL-3, IL-5 and GM-CSF, e.g., prevent proliferation of TF-1 cell in response to each of those cytokines amongst numerous other assays. The inventors also performed epitope mapping and found that the antibodies bound to CD131 within a region designated "Site 2" and also found that certain residues within Site 2 which are important for binding of IL-3, IL-5 and GM-CSF are also important for binding of the antibodies.

[0009] The inventors additionally showed that an antibody they had produced was capable of reducing survival of inflammatory cells from human subjects suffering from airway disease (e.g., asthma and/or nasal polyposis). This suppression in survival of inflammatory cells was greater than that observed using the current standard of care for inflammatory airway diseases, such as asthma (i.e., prednisolone). Using a xenograft model of nasal polyposis, the inventors showed that an antibody they produced reduced the size and weight of polyps and the number of B cells infiltrating polyps compared to a control antibody

[0010] The inventors also showed that neutralizing signaling of IL-3, IL-5 and GM-CSF is an effective manner of reducing survival of eosinophils, e.g., to treat eosinophilia. This was shown using an antibody of the disclosure that binds to CD131 or using a combination of antibodies against each of IL-3Rα, IL-5R and GM-CSF-R. While the combination of antibodies was effective in reducing survival of eosinophils, the antibody of the disclosure was more effective.

[0011] Based on the foregoing, it will be apparent to the skilled artisan that the inventors have produced a protein comprising an antigen binding domain of an antibody, the antigen binding domain capable of binding to or specifically binding to CD131 and neutralizing IL-3, IL-5 and GM-CSF signaling. The inventors have also produced methods for treating various conditions and/or reducing survival of eosinophils by neutralizing IL-3, IL-5 and GM-CSF signaling, e.g., using a protein of the disclosure.

[0012] In one example, the present disclosure provides a CD131-binding protein comprising an antigen binding domain of an antibody, wherein the antigen binding domain binds to or specifically binds to CD131 and neutralizes signaling by IL-3, IL-5 and GM-CSF, and wherein the CD131-binding protein inhibits GM-CSF-induced proliferation of TF-1 erythroleukemic cells with an IC_{50} of at least 700 nM.